REMARKS

Claims 1, 3, 6-8, 10, 13-14, 16-17, and 19-21 are pending in the application. In response to the Advisory Action mailed on July 31, 2003, claims 1 and 8 have been amended.

On September 8, 2003, Applicants' representatives participated in a telephone interview with the Examiner to determine whether the amended claims presented above are allowable. In the interview, the Examiner identified three references that she believed would anticipate or render obvious both the pending claims and the proposed amended claims. Applicants traverse.

The invention is not anticipated or obvious over the documents cited by the Examiner in the interview (U.S. Patent Nos. 5,750,651; 5,972,368; and 6,586,388). None of the patents, alone or in combination, teach or suggest a method for treating cartilage damage by administering an osteochondral graft.

U.S. Patent No. 5,972,368 ('368 patent) describes a deactivated bone graft in combination with bone morphogenetic proteins. It does not describe or suggest an osteochondral graft and does not indicate that the deactivated bone grafts it does describe would be useful for the regeneration of articular cartilage. Therefore, the '368 patent cannot render Applicants' invention anticipated or obvious.

U.S. Patent No. 5,750,651 ('651 patent) describes the combination of BMPs with a variety of matrices, made of synthetic materials or demineralized bone, for implantation into bone. In no way do these matrices resemble an osteochondral graft. Additionally, the '651 patent does not teach or suggest that these BMP-coated matrices

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would be useful for regenerating articular cartilage. Therefore, Applicants' invention cannot be rendered anticipated or obvious by the '651 patent.

U.S. Patent No. 5,586,388 ('388 patent) a member of the same patent family as the '651 patent, also describes the combination of BMPs with carrier matrices. These matrices are composed of demineralized bone or synthetic materials. The '388 patent does not describe or suggest the osteochondral grafts of Applicants' invention. Therefore, it cannot render the invention anticipated or obvious.

Claims 1, 3, 6-8, 13-14, 16-17, and 19-21 stand rejected as allegedly obvious over Hattersley and Pachence under 35 U.S.C. § 103(a). Applicants acknowledge that they inadvertently omitted claim 3 from arguments in the response to the Office Action mailed January 23, 2003, and respectfully request that all arguments regarding obviousness set forth in that response be applied to claim 3 as well.

The amended claims now recites methods and compositions for regenerating articular cartilage using an osteochondral graft treated with a composition consisting essentially of at least one BMP. Hattersley does not teach osteochondral grafts. Furthermore, it does not suggest that BMPs can be used with the osteochondral graft without PTHrP for regeneration of articular cartilage.

To establish a prima facie case of obviousness with a combination of references, it is not enough to establish that the two references, if combined, would anticipate the claims. Neither Hattersley nor Pachence anticipate the invention, and the requirement of the presence of PTHrP in the compositions of Hattersley prevent their combination from rendering the pending claims obvious because, as stated in Applicants' last response, it is well accepted that the omission of an element and retention of its function

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is an indication of unobviousness. *In re Edge*, 359 F.2d 896 (CCPA 1966); Manual for Patent Examining Procedure (2144.04).

The Examiner contends that one skilled in the art would be motivated to combine the teachings of Pachence and Hattersley with a high expectation of success as Hattersley allegedly teaches that BMP regulates bone and other tissue repair processes and Pachence allegedly teaches that osteochondral grafts can repair articular cartilage. Applicants disagree. The art must provide a perception of the problem to be solved by combination of the references. *Winner International Royalty Corporation v. Ching-Rong Wang*, 202 F.2d 1340 (Fed. Cir. 2000) (holding that the introduction of a ratcheting mechanism in a lock was not obvious over the disclosure that the mechanism was more convenient in a first reference, because there was no suggestion in the second reference that the original lock mechanism was not convenient enough). Pachence does not suggest any deficiency in its suggested solution to the problem of repairing articular cartilage. Similarly, Hattersley does not teach that the BMPs and PTHrP described therein, were not sufficient to solve the proposed problem. Without any perception of additional problems to be solved by the combination of the references, their combination is inappropriate.

The teachings of Pachence do not provide one skilled in the art with any reason to add a growth factor to the osteochondral grafts very briefly described in that specification. Even if there was a suggestion of the addition of growth factors, there is no suggestion that BMPs would be useful in the compositions of Pachence. Given the teachings of Pachence, one would have no reason to believe that BMPs would work in the disclosed osteochondral grafts.

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Additionally, Hattersley provides no suggestion or motivation to add its compositions to an osteochondral graft to regenerate cartilage. It also provides no suggestion to remove the PTHrP from its compositions. Therefore, Hattersley provides no suggestion of the continuing problem of regenerating articular cartilage that was solved by Applicants' invention of the combination of BMPs and osteochondral grafts. Accordingly, with no motivation to combine Hattersley and Pachence, there can be no prima facie case of obviousness and the rejection of the pending claims under 35 U.S.C. § 103(a) should be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: November 13, 2003

By: Elizabeth McNamee
Elizabeth E. McNamee
Reg. No. 54,696

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7. (Twice Amended) The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

14. (Twice Amended) The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

REMARKS

Claims 7 and 14 are amended to render the language of the claims more precise. Claims 1, 6-8, 10, 13-14, 16-17, and 19-21 are pending in the application. Attached is an appendix containing a version of the claims showing changes made by these amendments. For the convenience of the Examiner, a clean set of pending claims is also attached.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1, 6-8, 10, 13-14, 16-17, and 19-21 in condition for allowance. Applicants submit that the proposed amendments to claims 7 and 14 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner. Applicants further submit that entry of the amendment would place the application in better form for appeal, should the Examiner maintain the rejections of the pending claims.

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PATENT
Customer No. 22,852
Attorney Docket No. 08702.0068-00000

REJECTION UNDER 35 U.S.C. § 112

The Examiner rejected claims 7 and 14 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The Examiner specifically objects to the language "BMP-12 and members of the BMP-12 subfamily" as double inclusion. Claims 7 and 14 have been amended to remove this language, rendering the claims sufficiently precise to meet the requirements of 35 U.S.C. § 112, 2nd paragraph. Thus, Applicants request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 6-8, 10, 13-14, 16-17, and 19-21 are rejected as allegedly obvious ov r United States Patent No. 5,700,774 (Hattersley) in view of United States Patent No. 5,713,374 (Pachence). The Examiner states that Hattersley teaches a method and composition for repairing, reducing, or preventing damage to cartilage and cartilaginous tissue comprising administering a BMP together with PTHrP (parathyroid hormone recombinant peptide). The Examiner contends that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by combining the teachings of Hattersley with Pachence, which describes a method for anchoring tissue grafts into a cartilage defect. According to the Examiner, a motivation to combine the two references is the teaching in Pachence that osteochondral grafts or chondrocytes can be utilized for articular cartilage repair and/or regeneration. Applicants respectfully disagree with the Examiner's arguments.

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First, there is no motivation to combine the teachings of Hattersley and Pachence. The Examiner states "In-so-far-as Hattersley does not teach osteochondral graft, Pachence teaches a method to repair articular cartilage/regeneration which utilizes transplantation of osteochondral grafts and chondrocytes." This combination would require impermissible hindsight. Hattersley describes cartilage repair by administering growth factors. Hattersley does not provide any reason why one would want to or need to use an osteochondral graft for this purpose. Applicants note here that there are significant differences between cartilage grafts and osteochondral grafts, and enclose Miller, M., *Atlas of Chondral Injury Treatment*. Operative Techniques in Orthopaedics 7(4) 289-293 (1997) to demonstrate this point (see page 291). Pachence mentions that osteochondral grafts may be used for cartilage repair, but fails to provide any indication that these grafts would be suitable for use with a growth factor, let alone BMPs. It is only with the pending specification that one skilled in the art would know how to treat these grafts with BMPs and administer them to a patient. Therefore, it is only with impermissible hindsight that one skilled in the art could combine the teachings of Hattersley and Pachence to arrive at the claimed invention.

Even if a motivation to combine the reference exists, the combination of Hattersley and Pachence does not render the instant claims obvious. Hattersley teaches the use of BMPs in combination with PTH to induce cartilage regeneration. At best, a combination of the teachings of Hattersley and Pachence would produce grafts treated with both BMPs and PTH. Neither Hattersley nor Pachence provides any motivation whatsoever to remove an element, which Hattersl y defines as an essential

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factor in chondrocyte development and maturation, from this combination to achieve the claimed invention.[1] (See, Hattersley, Col. 1, line 66 - Col. 2, line 6.)

It is well accepted that the omission of an element and retention of its function is an indication of unobviousness. *In re Edge*, 359 F.2d 896 (CCPA 1966); Manual for Patent Examining Procesure (2144.04). Hattersley does not teach or even suggest that BMPs alone could be used to induce cartilage regeneration. As a result, Hattersley teaches away from the instant invention by indicating that PTH would be required in any composition comprising a BMP for the induction of cartilage regeneration.

In response to Applicants' previous arguments on this issue, the Examiner states that it is evident from Hattersley that the key ingredient is BMP (Office Action of June 17, 2002, page 8, lines 8-10). Applicants respectfully disagree with this characterization.

Contrary to the Examiner's contention, Hattersley makes it quite clear that PTH is a key ingredient of all compositions disclosed in the specification. Hattersley does not suggest that any of the various BMPs mentioned in the patent can be used without PTH for the regeneration of cartilage. In fact, Hattersley goes out of the way to specify that both BMP and PTH must be present in the methods and compositions described. See e.g., Col. 4, lines 26-30 ("The methods and compositions of the present invention may comprise simultaneous or sequential administration *of at least two active* agents, a TGF-β protein and a parathyroid hormone-related peptide, to a patient or site in need of cartilage repair, formation or manintenance.") (emphasis added). In view of this

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[1] Hattersley also teaches that chondrocytes are the tissue source for cartilage development.

disclosure, one of skill in the art would understand Hattersley to teach that PTH is as least as essential as BMP in the disclosed compositions.

It is only with hindsight and the instant specification that one skilled in the art would understand the relative importance of PTH and BMPs in the claimed methods. It is well established that employing such hindsight to reach a finding of obviousness is impermissible. Upon reading Hattersley, one would only know that is PTH an essential element in methods and compositions for the regeneration of cartilage. It is only with Applicants' disclosure that a skilled artisan would consider the feasibility of regenerating articular cartilage by administration of an osteochondral graft treated with a bone morphogenetic protein—in the absence of PTH—as is claimed by Applicants.

Accordingly, Applicant's request that the rejection under 35 U.S.C. §103(a) be withdrawn.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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(Hattersley, C I. 5.)

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Respectfully submitted,

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Dated: July 17, 2003

By: _____
Leslie A. McDonell
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Claims with Markings to Show Changes

7. (Twice Amended) The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, [~~members of the BMP-12 subfamily,~~] and MP52.

14. (Twice Amended) The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, [~~members of the BMP-12 subfamily,~~] and MP52.

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Clean Set of Pending Claims

1. A method for regeneration of articular cartilage comprising administering to an area in need of regeneration of said articular cartilage an osteochondral graft having applied thereto an amount of at least one purified bone morphogenetic protein (BMP) effective for the regeneration of said articular cartilage.

6. The method of claim 1 further comprising a protein which induces the formation of tendon or ligament tissue.

7. The method of claim 6 wherein said protein which induces the formation of tendon or ligament tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

8. A composition for regeneration of articular cartilage comprising an osteochondral graft having applied thereto an amount of at least one purified bone morphogenetic protein (BMP) effective for the regeneration of said articular cartilage.

10. The composition of claim 8 wherein said BMP is BMP-2.

13. The composition of claim 8 further comprising a protein which induces the formation of tendon or ligament-like tissue.

14. The composition of claim 8 wherein said protein which induces the formation of tendon or ligament-like tissue is selected from the group consisting of BMP-12, BMP-13, and MP52.

16. The method of claim 1 wherein said osteochondral graft is osteochondral allograft.

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17. The method of claim 1 wherein said osteochondral graft is osteochondral autograft.

19. The composition of claim 8 wherein said osteochondral graft is osteochondral allograft.

20. The composition of claim 8 wherein said osteochondral graft is osteochondral autograft.

21. A composition for the regeneration of articular cartilage said composition comprising an osteochondral graft having applied thereto an amount of BMP-2 effective for the regeneration of said articular cartilage.

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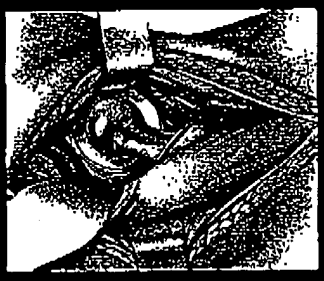

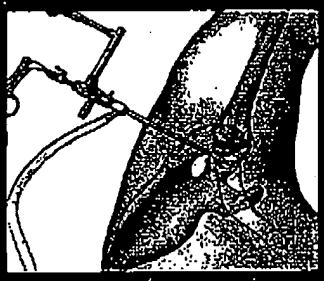

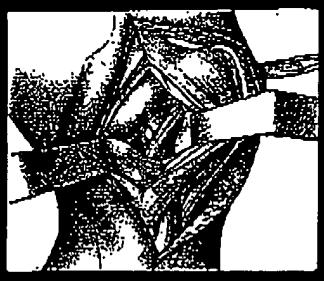

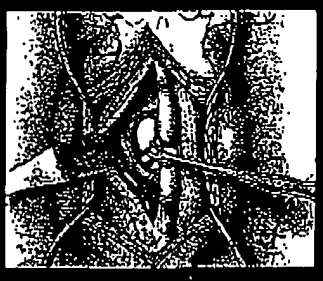

EDITOR
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TREATMENT OF CHONDRAL INJURIES

GUEST EDITOR
Mark D. Miller, M.D.

OPERATIVE TECHNIQUES IN ORTHOPAEDICS

Volume 7 Number 4 October 1997

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TREATMENT OF CHONDRAL INJURIES

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Volume 7 **Number 4** **October 1997**

ATLAS OF CHONDRAL INJURY TREATMENT

MARK D. MILLER, MD

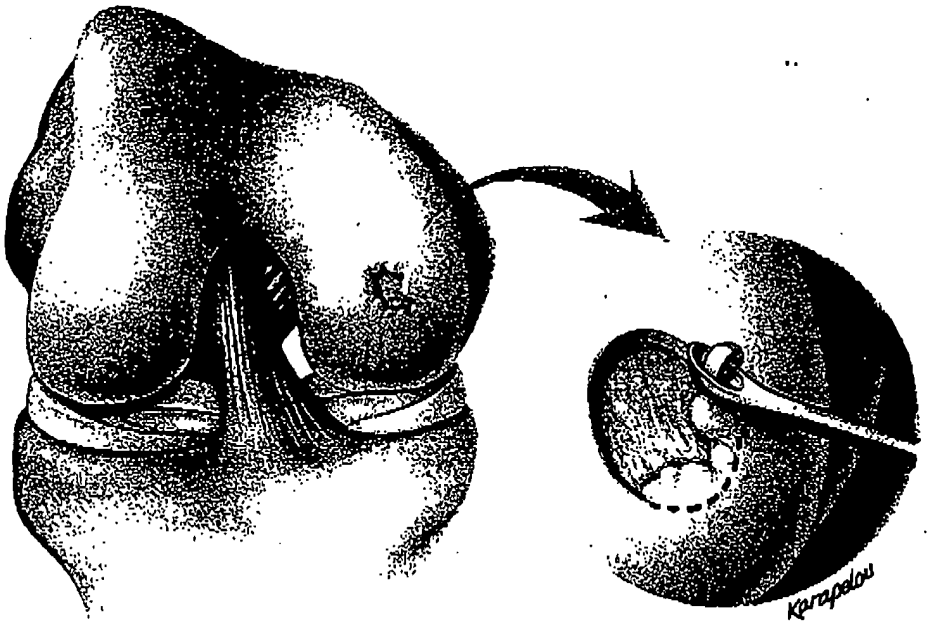

Fig 1. Most of the techniques presented in this journal are proposed for treatment of osteochondral lesions, commonly located on the Medial Femoral Condyle. Most techniques begin with debridement of the edges of the lesion as shown here.

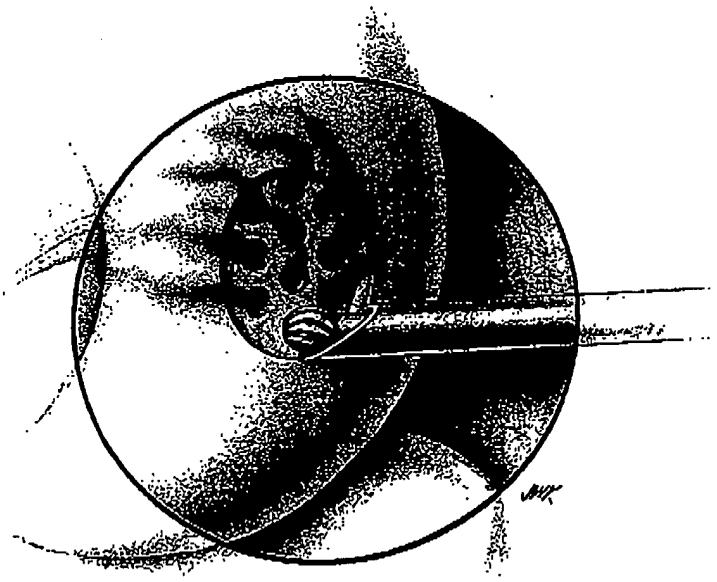

Fig 2. Abrasion Chondroplasty. This technique, popularized by Dr. Lanny Johnson, involves "abrasion" of the exposed subchondral bone to allow vascular ingrowth and stem cell production of fibrocartilage.

From Sports Medicine Service, Department of Orthopaedic Surgery, United States Air Force Academy, CO.

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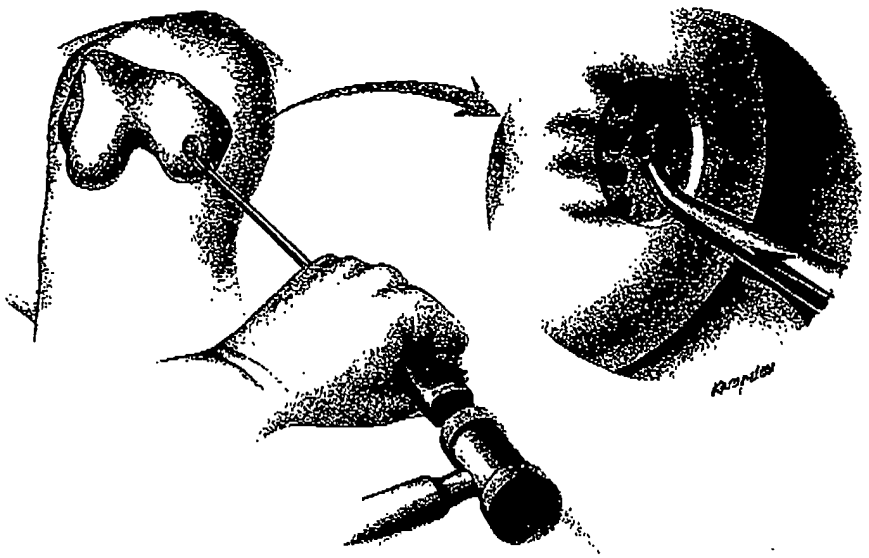

Fig 3. Microfracture. This technique, developed by Dr. Richard Steadman, is a variation of Abrasion Chondroplasty. Awls, with various degrees of angulation, are introduced through the ipsilateral arthroscopic portal and are used to penetrate the subchondral bone and encourage stem cell production of "cartilage-like" tissue.

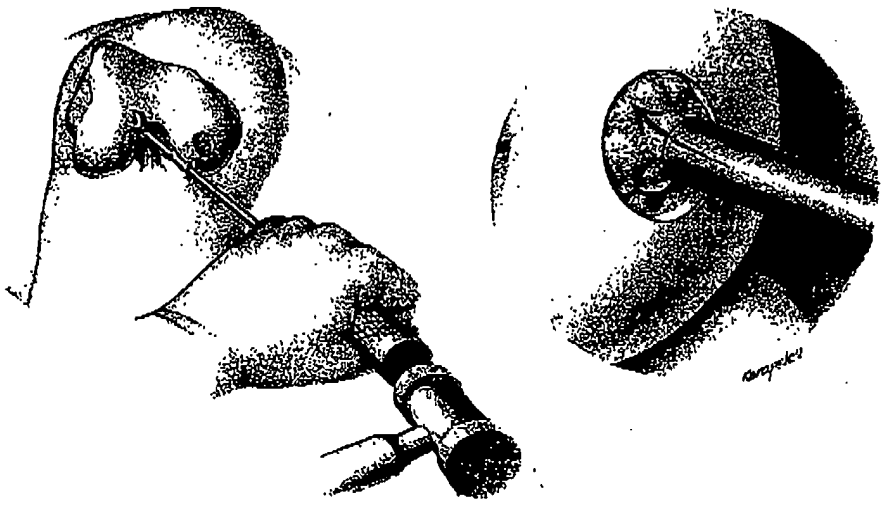

Fig 4. Slurry Grafting. This procedure has been proposed by Dr. Kevin Stone, and begins with defect preparation and microfracture. Next, bone and articular cartilage is harvested from the intercondylar notch and is run through a bone mill, creating a bone-cartilage "slurry." This is then introduced into the defect with a special plunger. According to Dr. Stone, the bone and cartilage reform their normal relationships and repair the defect.

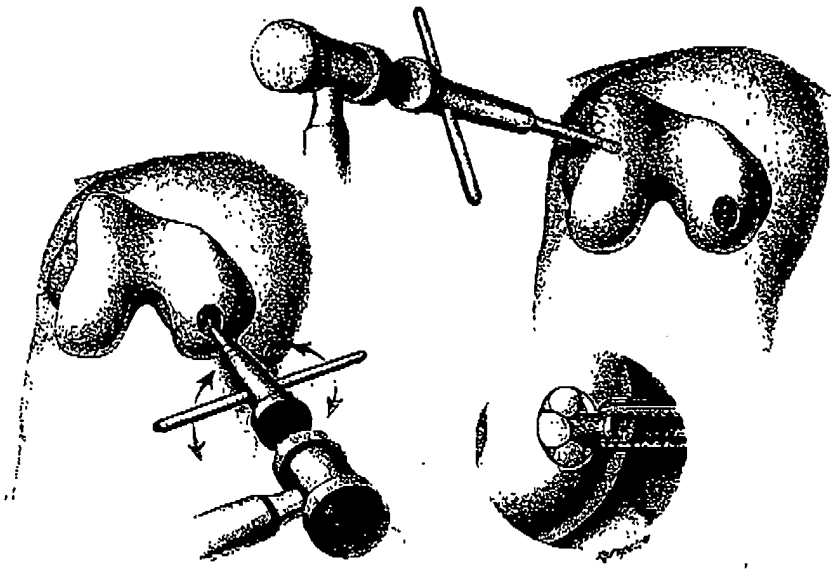

Fig 5. Osteochondral Plugs. There are at least three companies that have commercially available equipment for this technique, which is analogous to changing the pin position on a golf green. Cylindrical "plugs" of exposed bone are removed from the defect and plugs of normal nonweightbearing cartilage and bone are harvested and placed into the defect. Plugs can be created in various sizes and geometrically placed to maximally fill the area.

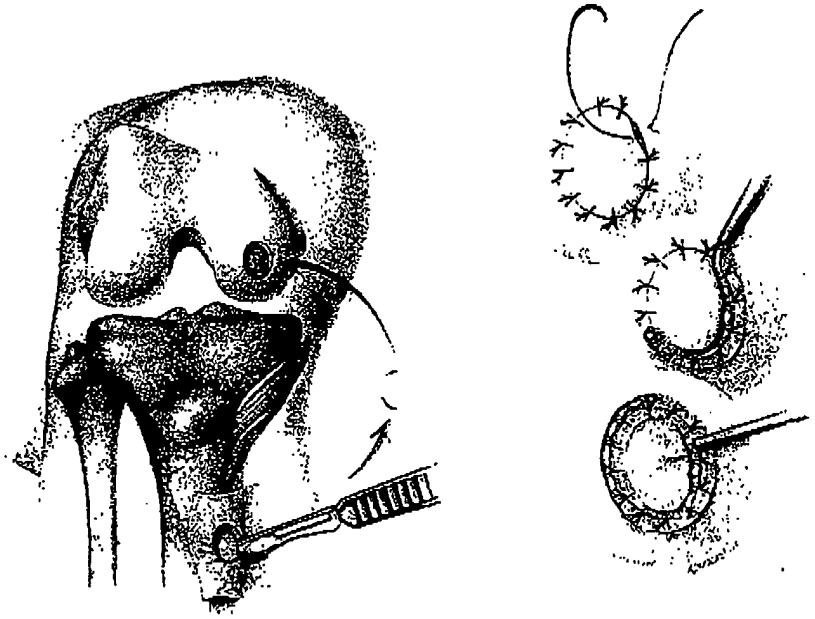

Fig 6. Chondrocyte Transplant. This technique, developed in Sweden, has received the most media attention and has generated a lot of excitement in the medical community and lay public. Articular cartilage is harvested arthroscopically from the nonweight-bearing area of the knee during the index procedure. This cartilage is sent to a laboratory where cartilage cells are "grown." A second open procedure is then completed several weeks or months later after the cells are available. Periosteum is harvested and sewn into the prepared defect with the cambium layer facing inward (A). Fibrin glue, which is prepared from a unit of the patient's own blood obtained at least 24 hours prior to the procedure, is used to seal the patch (B). The cartilage cell mixture is then injected under the patch (C), and is said to stimulate normal cartilage regeneration in the defect.

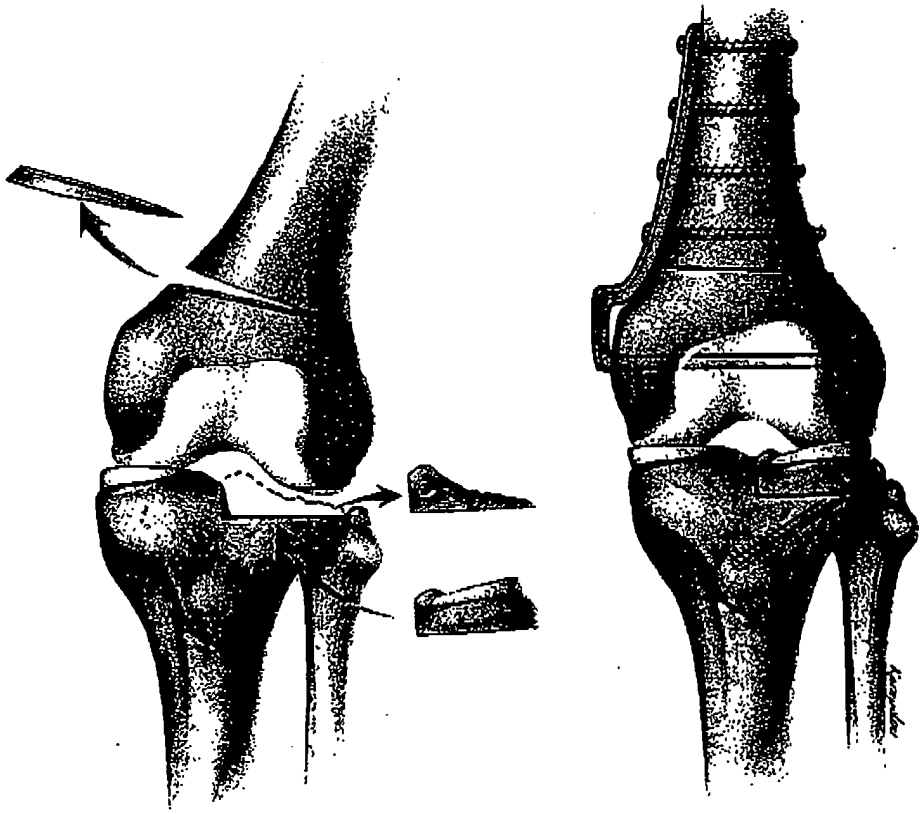

Fig 7. Osteochondral Allograft. This procedure, popularized by Dr. Allen Gross and Dr. John Garrett, involves transplantation of a *fresh* osteoarticular allograft into an excised area of injured cartilage and subchondral bone. An important part of this procedure is to correct the normal mechanical alignment of the joint.

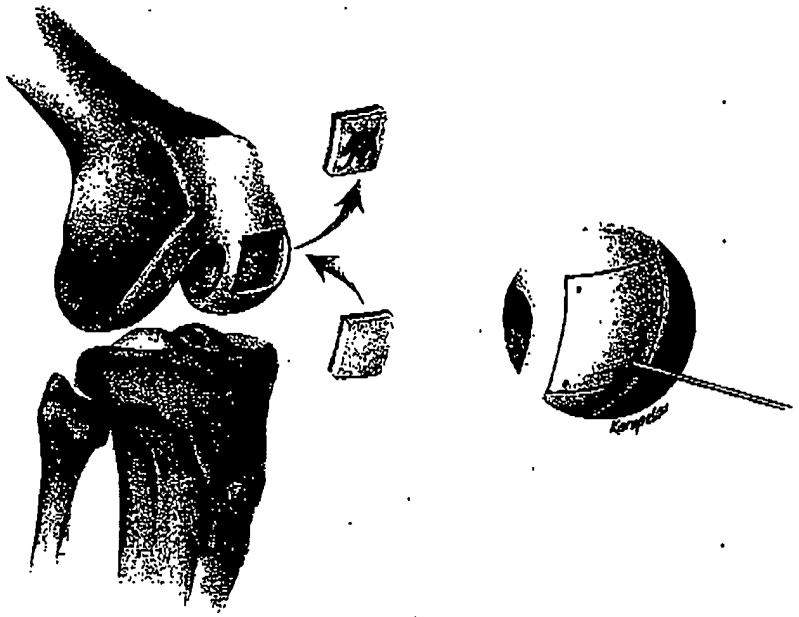

Fig 8. Shell Allograft. This procedure, developed by researchers in San Diego, is analogous to repairing a defect in your lawn with a piece of sod. The defect is excised and a matched fresh osteoarticular allograft is inserted into this area. It can be secured with mechanical interface or absorbable K-wires.

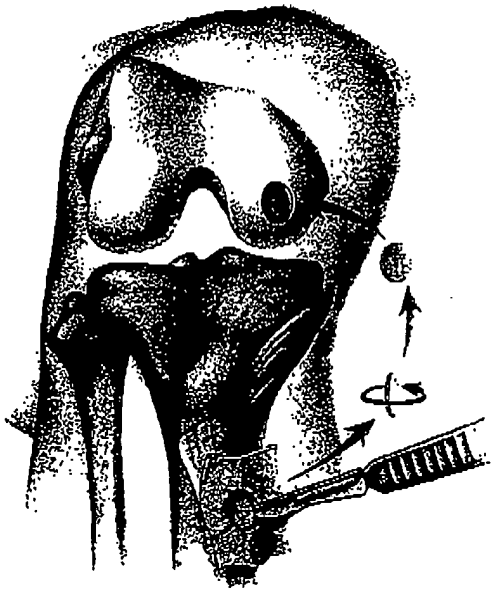

Fig 9. Periosteal Graft. This procedure, currently under investigation by Dr. Shawn O'Driscoll, is similar to the technique for fixing a puncture in an innertube. Periosteum is used for the "patch," but unlike the chondrocyte transplant technique, the inner cambium layer is rotated so that it is facing outward. The patch is carefully sewn in place and "cartilage" may grow out from the undifferentiated cambium layer of the graft.

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In Re Application of: ZHANG *et al.*

Application No.: 09/493,545 Group Art Unit: 1653

Filed: February 28, 2000 Examiner: Hope A. Robinson

For: METHODS AND COMPOSITIONS FOR HEALING AND REPAIR OF ARTICULAR CARTILAGE

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1. Petition for Extension of Time (1 page);
2. Request for Continued Examination (1 page);
3. Response and Amendment (7 pages); and
4. A check in the amount of $1,190.00.

Dated: November 13, 2003

Docket No.: 08702.0068-00000 (Due Date: 11/17/03)

LAM/EEM/kmb - Mail Drop CAMB